THE HAMNER INSTITUTES FOR HEALTH SCIENCES

# Science Question 3 – **Biologically relevant change in fetal testicular testosterone**

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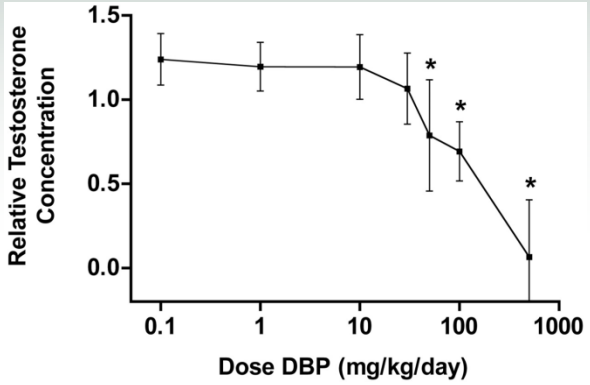
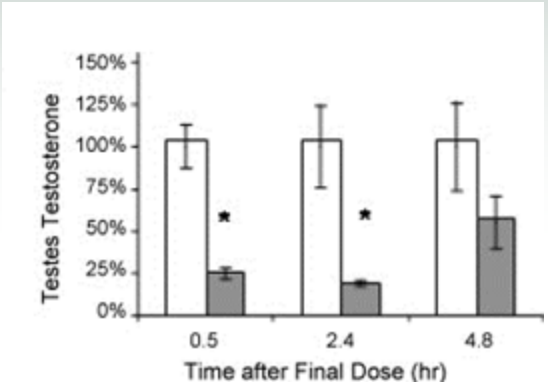
ACC High Phthalate Panel

# Inhibition of testosterone by phthalates

**500 mg/kg DBP →~ 75 - 90% inhibition**

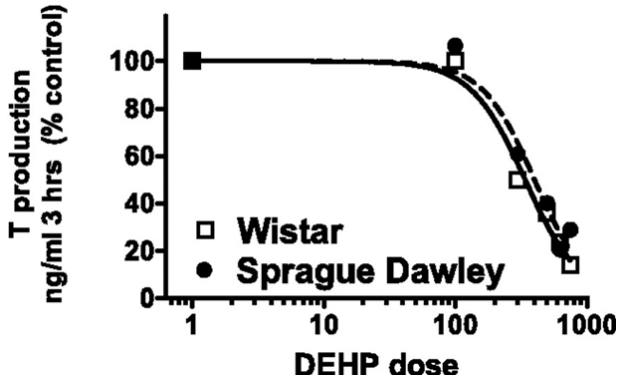



Lehmann et al. Toxicol. Sci. 2004;81:60-68, GD19



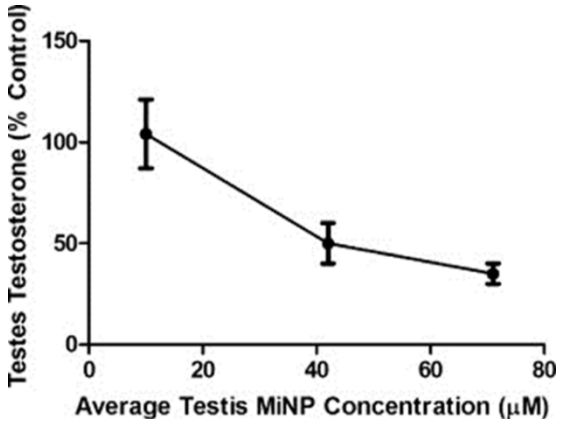

Clewell et al. Toxicology, Volume 255, Issues 1–2, 2009, 80, GD20

**500 mg/kg DEHP →~ 60 - 80% inhibition**




Hannas et al. Toxicol. Sci. 2011;123:206-216

**750 mg/kg DiNP →~ 75% inhibition**




Clewell et al. Reproductive Toxicology, Volume 35, 2013, 56 - 69

# Comparison of effects - DiNP Postnatal Study

| • 500 mg/kg/day DBP | • 750 mg/kg/day DiNP |
|---|---|
| – No body weight effects | – PND 2 body weight (750 mg/kg)<br>– PND 14 body weight (≥250 mg/kg) |
| – Nipple retention<br>– AGD (absolute and scaled) PND 2 + 14<br>– Phallus development<br>– Epididymal development<br>– Preputial separation<br>– Weight of 4 reproductive organs | – PND 14 reduced AGD (750 mg/kg) |
| – PND 2 ST – some enlarged tubules<br>– PND 2 #MNG/section, large LC aggregates<br>• Effects were seen to be transient (not observed at PND 49) | – No change in ST diameter<br>– PND 2 # MNG/section (≥ 250 mg/kg), large LC aggregates (750 mg/kg)<br>– Effects were seen to be transient (not observed at PND 49) |



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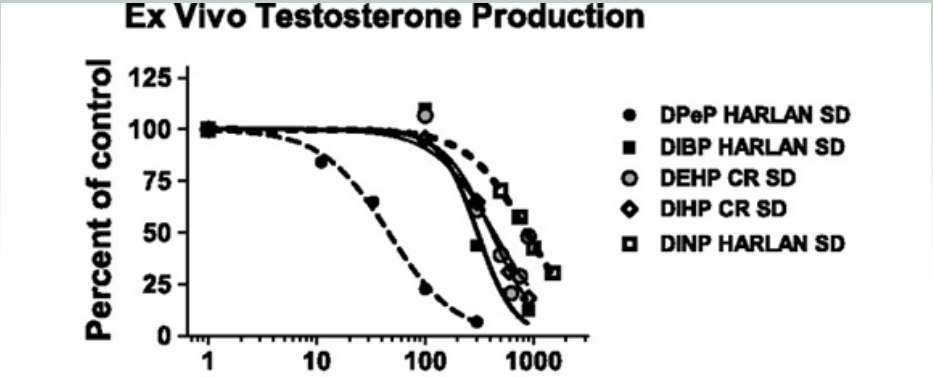
# Possible reasons for lack of malformations with DiNP

- Testosterone reduction is not sufficient to produce malformations (i.e., permanent effects).




Hannas et al. Toxicol. Sci. 2011;123:206-216

- Testosterone inhibition **alone** is not sufficient to induce downstream malformations.
  - Cryptorchidism, for example is a combination of testosterone and INSL3 reduction.
    - (Wilson et al., 2004)
  - Role of estrogen disruption in malformations?
    - Veeramachaneni and Klinefelter. Reproduction (2014) 147 435
- **More importantly…**
  - Species differences in phthalate effects.
    - (Johnson et al., 2012; Habert et al., 2014; Heger et al., 2012; Mitchell et al., 2012 )